Drug and Alcohol Dependence, 5 (1980) 341 - 356

ACUTE HEROIN ABSTINENCE IN MAN: I. CHANGES IN BEHAVIOR AND SLEEP*

RICHARD C. HOWE, FREDERICK W. HEGGE†, JERRY L. PHILLIPS

Department of Physiology, Eastern Virginia Medical School, Norfolk, Virginia 23501, and †Department of Military Medical Psychophysiology, Walter Reed Army Institute of Research, Washington, D.C. 20012 (U.S.A.)

(Received September 18, 1979)

Summary

The purpose of this study was to examine overt behavioral characteristics and sleep during acute heroin abstinence in man. Both heroin-dependent patients and drug-free control subjects were observed and monitored on a 24-hour per day basis for 5 to 7 days. Observational data were analyzed for frequency of occurrence of various behaviors including the signs and symptoms of withdrawal. Electroencephalographic (EEG) data were scored into awake and sleep stages according to standard techniques. The heroin-dependent subjects generally displayed a higher number of observations across all recording days as compared to the controls. In addition, the signs and symptoms of withdrawal for these patients peaked on day 1 or day 2 and then declined over the remaining recording days. The EEG state data showed an increase in waking and decrease in both slow wave and REM sleep during acute heroin withdrawal. Total sleep was maximally suppressed on withdrawal days 2 and 3 and was still below normal control values on withdrawal days 5 - 7. REM sleep was more disrupted than slow-wave sleep during withdrawal from heroin. Results of this study indicate that heroin withdrawal produces a differential action upon central nervous system structures responsible for the various states of sleep, waking and related behaviors.

Introduction

The process of drug dependence and withdrawal has been categorized into four basic stages. These categories include the drug initiation or induction phase during which increasing doses are administered and increasing tolerance and physical dependence develops to the drug. The drug mainte-

*Send reprint requests to: Dr. Richard C. Howe, Department of Physiology, Eastern Virginia Medical School, P.O. Box 1980, Norfolk, Virginia 23501, U.S.A.

nance or dose stabilization phase is related to chronic administration of the drug with a continued development of tolerance and physical dependence. The acute or early abstinence phase is associated with abrupt removal of the narcotic drug or administration of a narcotic antagonist. For heroin or morphine, this phase begins approximately 12 hours after the last dose and reaches a peak at 48 - 72 hours [1, 2]. After 2 - 3 days, the acute abstinence syndrome begins to subside and most of the grossly observable withdrawal symptoms return to more normal values in 7 - 10 days [1]. The final phase has been termed the protracted or secondary abstinence phase [1, 3] which follows the acute abstinence period and lasts 4 to 6 months. During this period, a number of physiological variables change to subnormal values [1]. The present study investigated the acute abstinence phase.

Previous human studies have not been able to record EEG or sleep data during the acute heroin or morphine withdrawal phase in chronically dependent patients [3 - 5]. This has been related to the uncooperative subjects and severity of the withdrawal syndrome reported in stateside drug users [1, 2, 4, 6]. In a study of chronic morphine intoxication, human sleep was recorded only during the predrug control, induction and dose stabilization phases [5]. Another study of morphine dependence and withdrawal examined several physiological parameters throughout the various phases of addiction, but used a gradual drug withdrawal regime over a three-week period [3]. Alterations in sleep have been reported with acute heroin administration in normal naive subjects [7]. However, in the study of Lewis *et al.* [7] heroin was administered only on three consecutive nights in four subjects and/or seven nights in only two subjects. Significant tolerance develops only when there is more or less continuous drug use [1]. Thus, the Lewis *et al.* [7] study was concerned with changes in sleep associated with the induction phase and did not involve heroin withdrawal from chronically dependent subjects. Other studies of methadone dependence were also not able to record the first sleep EEG until six weeks after the start of acute withdrawal [8, 9]. This was attributed to the "irritability, malaise and difficulty in sleeping" associated with methadone withdrawal in these patients [8]. To the best of our knowledge, the present study represents the first time that EEG sleep recordings and other electrophysiological parameters have been obtained in chronically dependent individuals during the acute phase of heroin abstinence.

The character and severity of withdrawal symptoms depend upon many factors including the particular drug, total daily dose, interval between doses, duration of use, health and personality of the drug-dependent individual [1]. Previous human withdrawal studies have been complicated in that heroin-dependent persons in the United States use a wide range of drugs concurrently, utilize the intravenous route of administration, use relatively impure heroin containing other pharmacologically active compounds and have complex drug and medical histories [10 - 12]. By contrast, the data collected in this study were from young healthy military personnel who were addicted to 92 - 98% pure heroin, used almost no other drugs concurrently, utilized primarily the nasopulmonary route of administration and had short histories

of heroin use [12 - 14]. In addition, abstinence symptoms were reported to be relatively mild in these young heroin users [15, 16] as compared to the more classic withdrawal syndrome described for stateside heroin users [1, 2]. This setting thus provided a good experimental model to evaluate heroin withdrawal without the many complications associated with stateside drug users.

The effect of opiate withdrawal on sleep in humans has not been examined during the acute withdrawal phase. However, other phases of the withdrawal syndrome have been studied. Kay *et al.* [17] found evidence of a delayed rebound excess of rapid eye movement (REM) sleep subsequent to the initial suppression resulting from an acute dose of morphine. After self-administration of heroin for three to seven days, Lewis *et al.* [7] reported a suppression of REM sleep and an increase in drowsiness or wakefulness during the drug administration period, and an increase in REM sleep during the protracted abstinence phase. During chronic administration of morphine, Kay [5, 18] noted that REM sleep decreased, waking increased and early slow-wave sleep decreased.

The effect of opiate drugs on the EEG and sleep has been more thoroughly examined in animals [19 - 29]. In morphine-dependent rats upon acute withdrawal, both the duration and mean EEG voltage output of REM sleep episodes declined to minimal levels the first day and remained below control levels up to the third day [20, 24]. This was followed by a rebound in REM sleep time above control levels up to the twelfth day. In the cat, a single dose of morphine was shown to increase wakefulness and to suppress both non-REM (slow-wave) sleep and REM sleep [21]. A decrease in slow-wave sleep has also been reported during cocaine withdrawal [27]. Khazan [22] observed an increase in slow-wave sleep during the first 4 - 6 hours of morphine withdrawal, followed by a progressive decrease in slow-wave sleep and increase in irritability.

The animal studies generally indicated a suppression of REM sleep during the acute morphine withdrawal phase [20, 24, 27, 29], whereas the human studies reported a long-term increase in REM sleep during protracted abstinence [7]. The slow-wave sleep data are considerably less clear. Furthermore, no investigations have examined the early effects of withdrawal from pure heroin or morphine on various sleep parameters in humans. Hence, the purpose of this study was to examine the effect of heroin withdrawal upon sleep and associated behavior during the acute abstinence phase in humans. Several preliminary abstracts on parts of these data have appeared [30, 31].

Methods

The objective of this research project was to analyze behavioral and electrophysiological data obtained from heroin dependent individuals during acute withdrawal. The electrophysiological parameters recorded in this study included the electroencephalogram (EEG), electrooculogram (EOG), electro-

cardiogram (EKG), electropneumogram (EPG) and electrogastrogram (EGG). All electrophysiological and behavioral observation data were collected on a 24-hour per day basis for 5 - 7 continuous days.

The recording environment was a typical hospital ward except that no visitors were allowed. Meals were served three times a day at 0650, 1120 and 1650 hours. Clinical evaluations and blood drawings were performed on all subjects three times daily at 0600, 1000 and 2200 hours for other aspects of this study [10 - 12]. After the initial 5 - 7 days of intensive monitoring, all patients were transferred to an adjacent ward for another week. This ward was concerned with a more traditional rehabilitation program (recreation, group therapy, work duties, *etc.*) in preparation for return to active duty. Blood drawings and psychological evaluations were continued on this ward.

Recording day 0 was defined as the day the subjects entered the study and day 1 as the first complete 24-hour day from midnight to midnight. Most of the subjects entered the study late in the afternoon or early evening on day 0. In-processing procedures required approximately two hours and included initial screening, consent form completion, medical history and physical, a shower, body and possessions search for illicit drugs and attachment of monitoring equipment.

The EEG data were recorded from twenty heroin-dependent patients and five drug-free control subjects and totalled 2602 hours of continuous recording time. Six of the drug-dependent patients voluntarily withdrew during the study. The demographic data and heroin use history for some of the drug users have already been published [10, 12]. Briefly, the heroin-dependent patients had a mean age of 20.3 years, had used heroin for approximately 3.8 ± 1.6 months before entering the study and had an average total daily intake of 973 mg of heroin. Route of administration for these patients was primarily smoking as an admixture with tobacco or forceful inhalation of the white crystalline drug into the nostrils, although two subjects administered the drug intravenously.

In the body, heroin (diacetylmorphine) is rapidly hydrolyzed to monoacetylmorphine (MAM) which, in turn, is hydrolyzed to morphine [32]. As heroin and MAM are more effective in crossing the blood–brain barrier, heroin is 2.5 times more potent than morphine on a weight basis [33]. Heroin is also primarily excreted as free or conjugated morphine (morphine-3-monoglucuronide) in the urine [32]. The median urine morphine concentration of the patients in this study on day 0 (admission) was 20.4 ± 7.6 μg/ml [10]. The nasal inhalation and intravenous heroin users had equal urine morphine concentrations on admission. The patients who administered heroin by smoking had lower urine morphine concentrations on day 0 than the other two groups. However, no significant urine morphine differences were found on day 1 through day 6 for these three groups of heroin users [12].

As no drugs were given throughout this research project, an attempt was made to secure the drug-dependent patients as soon as possible after they had self-administered their last dose of heroin. Thus, these patients

entered the study approximately 1.6 ± 1.1 hours after self-administration of the drug, and 78% of the patients entered in less than one hour since their last dose. The average last dose was estimated from patient histories to be 332.5 mg of 92 - 98% pure heroin. Patients were selected from heroin users identified in the Army drug-screening program. All patients studied were covered by the provisions of the Army Exemption Policy which established voluntary rehabilitation programs for drug users. Informed consent was obtained from all patients and matched controls who participated in this project. The control subjects had a mean age of 22.2 years and used no drugs except for an occasional alcoholic beverage and/or marijuana.

All electrophysiological data were obtained via a telemetry system (Lexington Model A120), recorded on a magnetic tape recorder (Tandberg Series 100), and subsequently played back onto paper records for manual scoring. In order to save on the number of telemetry channels and attached electrodes, a monopolar EEG lead was referenced to an EOG lead. The EEG and EOG electrodes were standard gold cup electrodes (Grass) and were affixed to the skin by a small gauze patch covered with collodion. Standard sleep EEG records are obtained from electrodes placed at the C3 or C4 positions and referenced to an indifferent ear electrode on the contralateral side. However, in this study, the detection of wakefulness was just as important as sleep, especially during early withdrawal where it was anticipated that sleep would be suppressed and wakefulness enhanced. The alpha rhythm, an 8 - 12 Hz EEG pattern recorded primarily from the occipital cortex, is associated with an awake individual usually with eyes closed. It was expected that during early withdrawal the patients would attempt to sleep but would be unable to; *i.e.* would be in bed with eyes closed but still awake. The best approach in evaluating this state was to record the alpha rhythm. Therefore, the EEG electrode was placed over the occipital cortex in the standard 0-2 position from which both alpha rhythm and general EEG patterns could be recorded. The EEG records from the control subjects were used to verify this EEG recording set-up. The EOG electrode was placed 1 cm beyond the lateral orbital ridge of the right eye. The EEG and EOG also detected EMG activity from the head muscles.

Therefore, EEG, EOG and EMG were multiplexed on the same data channel. As the frequency range of EMG is considerably higher than EOG and EEG, bandpass filtering was performed during playback of these data onto paper records in order to remove the EMG activity. Further separation of EOG and EEG activity by filtering is not possible, as their frequency bands overlap. However, amplitudes of these physiological parameters differ considerably in that EEG is in the microvolt range and EOG is in the millivolt range. By decreasing the gain during playback, it was possible to retain the EOG activity while totally suppressing all EEG signals. During playback of the multiplexed signals from magnetic tape to paper records, three channels were recorded: (1) the raw unfiltered multiplexed signal with EMG, (2) the filtered EEG channel with EOG, and (3) the filtered EOG channel. Standard sleep EEG records contain one EEG channel, two EOG channels,

and an EMG channel [34]. However, the usefulness of the EMG in scoring sleep states has been criticized recently as it tends to be more closely associated with body position rather than with sleep stages. Hence, the EEG records in this study consisted of one EEG channel, one EOG channel, and some EMG.

In addition, continuous behavioral observations were noted on "subject log sheets" throughout the entire recording time (5 - 7 days). Time of day and tape recorder footage were noted on the log sheets for each behavioral observation. An observation was noted only when it differed from the previous one. The types of observations noted on the subject log sheets were gross behavioral activities easily seen at a distance, such as in bed, out of bed, awake, asleep, walking, talking, sitting, eating, drinking, smoking, reading, *etc.* Playing guitar quietly, watching television, looking around, reading, looking at books and listening to tapes were all scored as quiet. Singing, playing cards and talking, and answering questions were all scored as talking. Semi-supine and reclined or semi-reclined were scored as supine. Any gross clinical withdrawal symptom, such as yawning, sneezing, blowing nose, vomiting, or restlessness, was also entered on the log sheets. Toss in bed and toss and turn were scored as restless. Urination and/or defecation were scored as excretion. Any other types of ward or patient disruption, such as loud noises, visitors, changing of electrodes, were likewise noted. All behavioral observations were totaled, meaned and tabled for each complete 24-hour recording day.

The EEG records from all subjects were manually scored into the standard awake and sleep states [34] in 1-minute epochs. These states included awake, awake with alpha rhythm, sleep stages I, II, III, and IV, and REM sleep. An "undefined" category was also used for those time intervals where the EEG signal was missing or uninterpretable. The "awake with alpha" state was analyzed due to the appearance of long trains of alpha rhythm associated with the heroin-dependent persons lying in bed awake with eyes closed. This behavioral category was substantiated by the subject log sheets. REM sleep was scored from the first eye movement to the last eye movement or to an abrupt movement artifact associated with waking behavior. Independent reading and cross-checking of the scored data were also performed in order to verify interscorer reliability. The raw minute-by-minute EEG data were first punched onto paper tape using an appropriate alpha-numeric code for each behavioral state, transferred to the computer (PDP8E) into 24-hour data blocks (1440 data values per day), and then plotted for visual inspection of the behavioral state changes. The raw EEG data were used to calculate total minutes of the various sleep–waking states. Only complete 24-hour days were used in the data analyses.

Results

Behavioral observations

The results of this section were based on analysis of the subject log sheets where continuous behavioral observations were noted throughout the

entire five to seven day recording time. As mentioned earlier, the majority of the heroin-dependent subjects self-administered their last dose within one hour of entering the study and most of the subjects entered late in the afternoon or early evening on day 0. After completion of the in-processing procedures, most of the heroin-dependent patients were in bed and displayed "narcotic high" or "nodding out" behaviors. Early observations for these subjects on day 0 were quite similar to the controls except that the controls showed more active behaviors (walking, sitting, out of bed, awake) whereas the heroin-dependent patients displayed more inactive behaviors (quiet, prone, in bed, sleep).

A summary of the behavioral observations for recording days 1 through 5 is presented in Table 1 for the heroin-dependent subjects and in Table 2 for the control subjects. These tables represent the mean number of observations recorded per 24-hour day per behavioral category. Only those observations significantly different between the heroin users and controls were included in these tables. In the heroin-dependent patients during withdrawal, the following observations peaked on day 1: awake, prone, restless, rolling, sneezing, stretching, and supine. Of these observations, the following categories displayed a decreasing trend across withdrawal days 1 through 5: restless, rolling, sneezing, and stretching. The categories drinking and lateral decubitus peaked on day 2 of withdrawal and then showed a decreasing trend through withdrawal day 5. The following observations peaked during the latter part of the acute withdrawal phase on days 4 and/or 5:eating, excretion, in bed, out of bed, sitting, talking and walking. On days 2 and 3 of withdrawal, the eating category was lowest whereas drinking was highest. The talking and walking categories were lowest on withdrawal days 1 and 2.

The observations for the control subjects were generally highest on recording days 1 and/or 5, next highest on day 4 and lowest on day 3 (Table 2). The mean number of observations was considerably lower in the control subjects than in the heroin-dependent patients. The following behavioral categories showed the greatest mean difference between the heroin users and controls: prone, restless, rolling. The categories that showed the next largest differences included drinking, excretion, lateral decubitus, stretching, and supine.

Sleep

All EEG records were scored and analyzed on a 24-hour per day basis. As mentioned above, each recording day was defined from midnight to midnight. Visual examination of the EEG state plots on day 1 revealed that sleep of the control subjects was generally shortened and more disrupted (Fig. 1A). These changes were related to the typical "first night effect". As most of the heroin-dependent patients entered the study within one hour of self-administration of their last dose, they generally did not begin withdrawal until midway through day 1. Thus, the heroin-dependent patients slept and/or "nodded out" through the last part of day 0 and the first part of day 1. These patients generally displayed more total sleep on day 1 than

TABLE 1

Behavioral observations in heroin-dependent patients across withdrawal days 1 - 5. Each data value is the mean number of observations per 24-hour period. The statistical data (right side) were calculated relative to the behavioral observations in the controls (see Table 2)

Behavioral observations	Day 1	Day 2	Day 3	Day 4	Day 5	Mean of days 1 - 5	*p* value	Mean of days 2 - 5	*p* value
Definitely awake	4.4	3.7	2.6	3.0	2.9	3.3	0.01	3.1	0.01
Drinking	4.3	6.5	6.2	4.8	4.5	5.3	0.001	5.5	0.001
Eating	6.9	6.2	6.1	7.0	6.9	6.6	0.01	6.6	0.05
Excretion	7.0	8.8	8.4	8.9	8.7	8.4	0.001	8.7	0.01
In bed	20.1	20.5	19.6	21.7	21.8	20.7	0.001	20.9	0.001
Lat. decubitus	25.1	28.0	16.1	15.8	14.7	19.9	0.01	18.7	0.02
Out of bed	20.0	20.5	19.8	20.8	21.4	20.5	0.001	20.6	0.001
Prone	9.3	6.4	5.9	5.5	5.9	6.6	0.001	5.9	0.001
Restless	9.5	8.5	4.8	1.0	2.0	5.2	0.02	4.1	0.05
Rolling	41.6	39.1	24.0	24.2	23.0	30.4	0.01	27.6	0.01
Sitting	29.8	30.4	31.7	31.2	32.0	31.0	0.01	31.3	0.01
Sneezing	2.4	2.1	1.1	1.0	0.2	1.4	0.01	1.1	0.05
Stretching	2.2	1.5	1.4	1.0	1.1	1.4	0.01	1.3	0.01
Supine	26.2	24.5	15.9	16.7	16.9	20.0	0.01	18.5	0.01
Talking	13.1	12.6	16.6	16.5	16.6	15.1	0.01	15.6	0.05
Walking	29.9	35.3	38.7	41.5	39.0	36.9	0.01	38.6	0.01

TABLE 2

Behavioral observations in control subjects across recording days 1 - 5

Behavioral observations	Day 1	Day 2	Day 3	Day 4	Day 5	Mean of days 1 - 5	Mean of days 2 - 5
Definitely awake	2.3	2.0	1.7	2.0	1.7	1.9	1.9
Drinking	2.7	1.7	2.3	2.3	2.7	2.3	2.3
Eating	5.7	5.3	6.0	5.0	3.7	5.1	5.0
Excretion	5.7	6.3	3.3	4.7	4.0	4.8	4.6
In bed	16.3	12.7	12.3	12.7	15.0	13.8	13.2
Lat. decubitus	7.7	6.0	8.3	7.7	10.3	8.0	8.1
Out of bed	15.7	13.0	11.7	12.3	15.0	13.5	13.0
Prone	1.0	1.7	1.7	2.0	3.0	1.9	2.1
Restless	0	0	0	0	0	0	0
Rolling	11.0	7.3	13.0	12.0	13.0	11.3	11.3
Sitting	28.3	21.0	16.7	23.3	28.0	23.5	22.3
Sneezing	0	0	0	0	0	0	0
Stretching	1.0	0	0	0.3	0.7	0.4	0.3
Supine	10.0	5.3	9.0	8.7	10.0	8.6	8.3
Talking	7.3	11.7	6.0	11.7	11.7	9.7	10.3
Walking	29.3	25.6	22.3	28.7	29.7	27.1	26.6

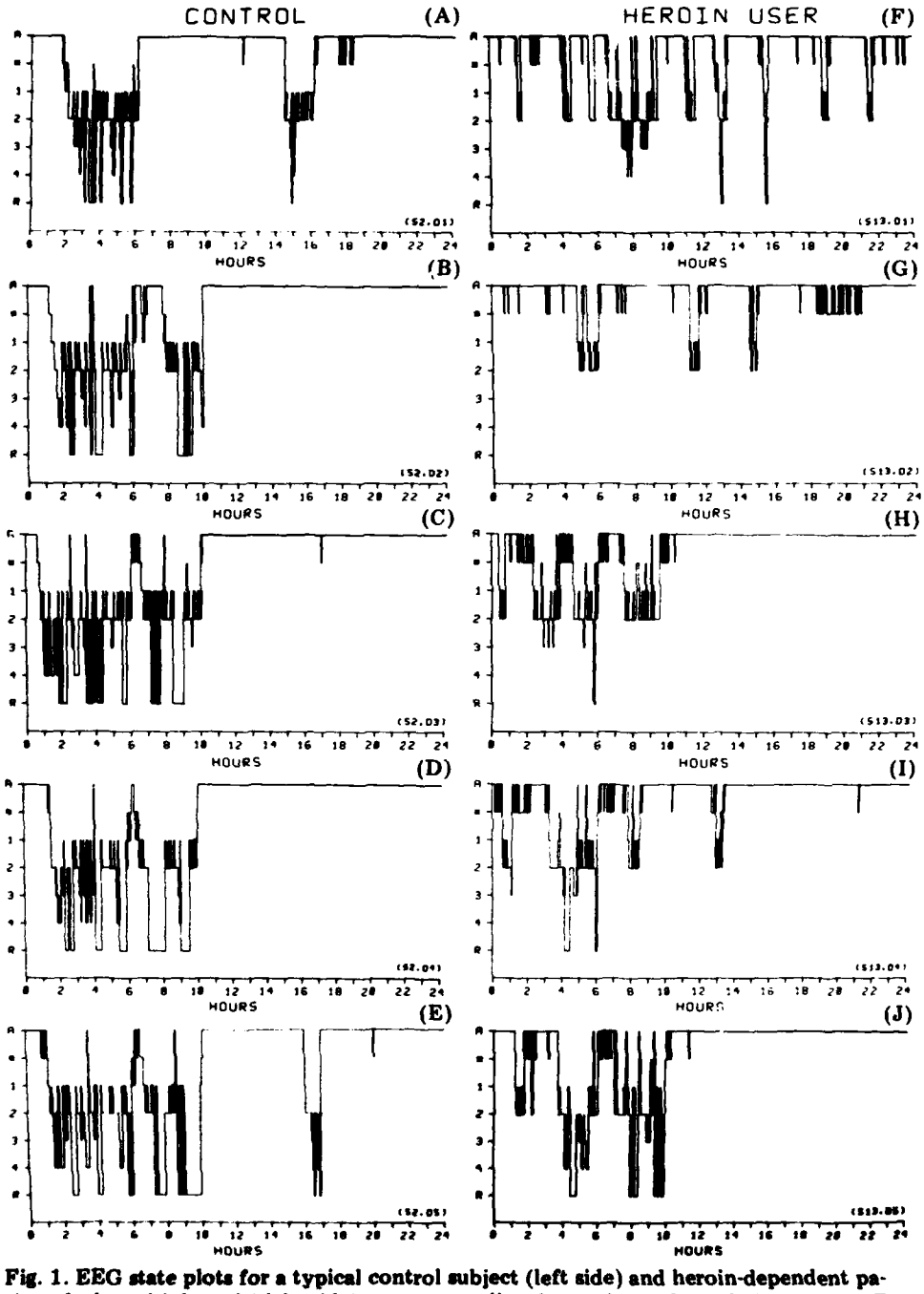

Fig. 1. EEG state plots for a typical control subject (left side) and heroin-dependent patient during withdrawal (right side) across recording days 1 (top) through 5 (bottom). Frequent state changes are indicated by the darker areas. Note the marked disruption in sleep on day 2 of withdrawal in the heroin-dependent patient (G) and gradual increase in sleep in this subject during subsequent days.

the controls, although sometimes the sleep was dispersed throughout the day (Fig. 1F).

The EEG state plots of the heroin-dependent patients showed considerable disruption of sleep on days 2 and 3 (Fig. 1G and H). Most of the heroin-dependent patients displayed the maximum sleep disturbances on day 2. Even though less disruption of sleep was observed on days 4 and 5, the heroin-dependent patients still showed considerably abnormal sleep–waking patterns (Fig. 1I and J).

In the control subjects, the EEG state plots showed more normal patterns during recording days 2 - 5 (Fig. 1B - E) with some apparent adaptation to the hospital ward environment continuing through day 3 or 4. The plot shown for subject 2, day 4 (Fig. 1D) was typical of most of the control subjects who generally slept from some time after midnight until the 10 a.m. clinical evaluation. The waking behavior at 0600 hours each day was associated with the 6 a.m. clinical evaluation, after which the controls generally returned to sleep. Some of the controls also displayed afternoon naps, similar to that shown in Fig. 1E.

In order to determine whether any significant differences were present across recording days in each group, within-group comparisons were performed on total awake and total sleep (paired observation t-test). These analyses revealed that total awake and total sleep on day 1 in the drug user group were significantly different from those on the next four recording days ($p < 0.001$). Total awake and total sleep were not significantly different among recording days 2 - 5 in the heroin-dependent patients. The controls showed no significant difference in total awake and total sleep between any of the recording days, except for paired days 3 and 4 ($p < 0.01$). This difference was attributed to random fluctuation in variances and is probably not of great importance. In order to avoid the "first night effect" in the controls on day 1 and the increase in sleep and decrease in waking in the heroin-dependent patients on day 1, the mean data presented below were from recording days 2 through 5.

The drug-dependent subjects displayed a mean total awake value of 1135.8 minutes per 24-hour day during heroin withdrawal, whereas the controls averaged 984.1 minutes of waking during this same period (Table 3). A graph of the total awake values for both heroin-dependent patients and controls across days is displayed in Fig. 2 (top). As shown in this figure, total awake on day 1 was less in the heroin-dependent subjects than in the controls. Total awake then exceeded the control values in the heroin user group across withdrawal days 2 - 5. The drug-dependent patients showed a mean total sleep value of 304.2 minutes per 24-hour day during withdrawal compared to 455.9 minutes in the controls (Table 3). As shown in Fig. 2 (bottom), total sleep in the heroin-dependent patients on day 1 exceeded the control values. The drug patients then showed a marked decrease in total sleep below control values during withdrawal days 2 - 5. Both total awake and total sleep differences were significant at the $p < 0.001$ level (two-tailed t-test between groups, population variances unknown but assumed equal).

TABLE 3

Average total minutes per 24-hour day of sleep–waking states in heroin-dependent patients during withdrawal and in control subjects. Mean values were averaged across recording days 2 - 5

Behavioral state	Heroin users		Controls		
	Minutes (24-hour day)	Percentage	Minutes (24-hour day)	Percentage	p* (two-tailed)
Total awake[a]	1135.8 ± 10.9	78.9	984.1 ± 32.3	68.3	<0.001
Total sleep[a]	304.2 ± 10.9	21.1	455.9 ± 32.3	31.7	<0.001
Awake with alpha[b]	71.2 ± 19.7	6.3	39.6 ± 7.8	4.0	<0.05
Stage I[c]	57.9 ± 8.3	19.0	67.1 ± 2.1	14.7	<0.10
Stage II[c]	175.9 ± 5.6	57.8	234.8 ± 24.4	51.5	<0.01
Stage III[c]	24.0 ± 4.4	7.9	30.8 ± 3.8	6.8	<0.10
Stage IV[c]	17.6 ± 7.2	5.8	28.9 ± 10.4	6.3	NS
REM[c]	28.8 ± 5.2	9.5	94.3 ± 15.6	20.7	<0.001

*Addicts versus controls, minutes, recording days 2 - 5.
[a]Percentage column based on 24-hour day.
[b]Percentage column based on total awake.
[c]Percentage column based on total sleep.

The mean values for the remaining waking and sleep states across recording days 2 - 5 are presented in Table 3. The heroin-dependent patients during withdrawal showed 71.2 minutes of awake with alpha per 24-hour day, whereas the control subjects had 39.6 total minutes per day ($p < 0.05$). Stages I, II, III and IV sleep were generally reduced in the heroin-dependent patients during withdrawal, although only stage II sleep was significant ($p < 0.01$). Total average minutes per 24-hour day for stages I, II, III and IV during acute heroin withdrawal were 57.9, 175.9, 24.0 and 17.6 minutes, respectively. This compares to 67.1, 234.8, 30.8 and 28.9 total minutes found in the control subjects for sleep stages I - IV, respectively. REM sleep averaged 28.8 total minutes per day in the heroin-dependent subjects during withdrawal, whereas the controls averaged 94.3 total minutes for the same period ($p < 0.001$).

Discussion

A major problem of morphine and/or heroin research in humans has been the uncooperativeness, irritability, and general malaise related to the withdrawal syndrome [1, 2, 8, 9]. Thus, studies to date have not been able to record electrophysiological parameters during the acute withdrawal phase. The subjects in this study, however, overtly exhibited a milder clinical withdrawal pattern as compared to the classical picture of withdrawal [1, 2]. This has been reported in other epidemiological studies of heroin use in

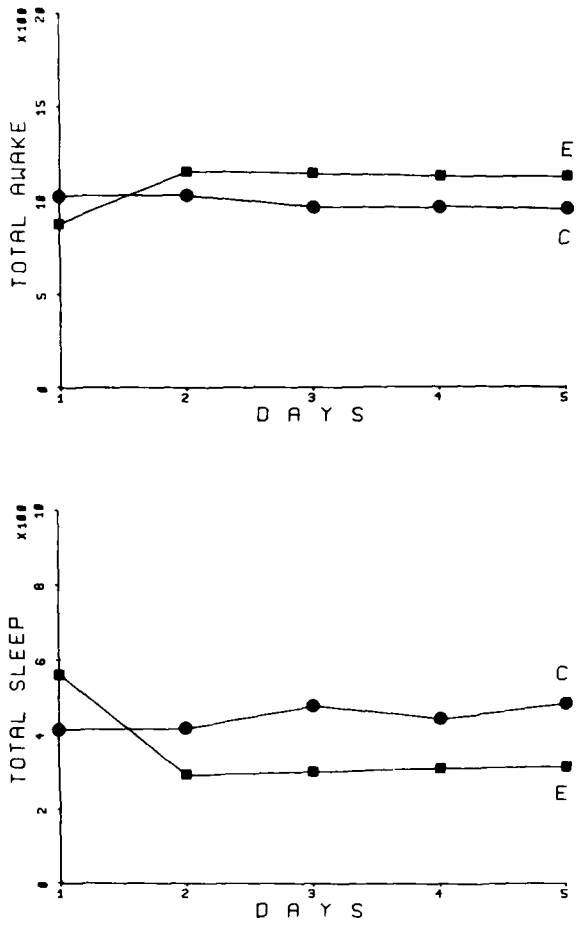

Fig. 2. Plot of total awake (top) and total sleep (bottom) across recording days 1 - 5. Control subjects (C) are plotted with circles and heroin-dependent patients (E) with squares. Vertical axis represents total minutes per day. Note the increase in waking and decrease in sleep in the heroin-dependent patients across withdrawal days 2 - 5.

military personnel [15, 16, 35]. These differences may be attributed to the relatively short exposure to heroin (4 months), good health and nutritional status, young age, and use of the nasopulmonary route of administration in the majority of the subjects in this study. However, regarding the route of administration, no significant differences were found on day 1 through day 6 in urine morphine concentrations between the intravenous and nasopulmonary users in this study [12].

Another possible cause relevant to the milder abstinence syndrome for the patients in this study may be the administration of a relatively pure versus impure mixture of the drug. Common streetside "heroin" is relatively impure (3 - 10% heroin) and is mixed with many types of pharmacologically

active compounds, which may themselves contribute to the withdrawal syndrome. Finally, the subjects in this study were relatively naive to the withdrawal phenomenon and did not overtly express the conditioned or learned fear of withdrawal commonly present in drug-dependent civilians [36]. Thus, the milder withdrawal syndrome and cooperativeness of most of the patients permitted us to monitor and record various electrophysiological parameters on a 24-hour per day basis during the acute withdrawal phase.

In spite of the milder withdrawal syndrome exhibited by our patients, the withdrawal signs and symptoms and time course of these events were similar to those reported in the civilian addict population [3]. The opiate administration phase has been characterized by such behavioral traits as lessened physical activity, lethargy, drowsiness, and sleep [32]. As most of the drug-dependent patients entered this study shortly after taking their last dose, the early behavioral observations similarly reflected the "narcotic high" or "nodding out" behaviors as noted above.

Behavioral characteristics noted in animals during withdrawal have included an increase in aggression [37], hyperirritability [38] and an increase in motor activity [39]. Similar characteristics of restlessness, irritability and tremor have been reported during heroin or morphine withdrawal in humans [1]. The results of this study similarly confirm these earlier behavioral characteristics of opiate withdrawal. However, most of the subjects in this study did not show the nausea and/or vomiting that has been reported to be associated with narcotic withdrawal [1]. This again may reflect the milder withdrawal pattern exhibited by the patients in this study versus the civilian addict population. Analysis of the gastric activity recorded in this study may provide more definitive information on the gastrointestinal activity.

Regarding the time course of acute withdrawal, the withdrawal signs and symptoms peaked on day 1 or day 2 and then decreased throughout the remaining observational days. This is similar to that reported in the civilian addict population [1]. However, the time course of morphine withdrawal in experimental animals is somewhat different. In rats, there is an initial depressed state for the first 4 - 6 hours with an increase in behavioral sleep, followed by a secondary agitated state across withdrawal days 1 - 3 [22, 40]. Behavioral characteristics of this secondary agitated state have included hyperirritability, tremor, piloerection, ptosis, diarrhea, "wet dog shakes" and a marked decrease in sleep [22, 40]. Overt behavior in these experimental animals appears normal by withdrawal days 4 - 5. In the present study, most of the withdrawal signs and symptoms were still present and elevated on withdrawal day 5. This suggests that the acute withdrawal phase continues beyond this time frame in humans.

In comparison with the EEG state data, the behavioral data showed the highest number of "awake" observations in the heroin-dependent subjects on day 1, whereas the EEG state data showed more total awake (in minutes) on recording days 2 - 5. The behavioral data may be related to the greater restlessness and rolling and subsequent "awake" observations recorded on day 1, even though the total amount of the awake category (in minutes) was

less than on the following days. The decrease in total waking on day 1 in the drug-dependent patients was related to the "nodding out" and associated sleep observed in these patients during the early part of day 1. The heroin-dependent subjects also had more frequent "awake" observations than the controls across all recording days. The EEG state data from days 2 - 5 similarly showed more total waking in the drug-dependent group.

The increase in waking during the early part of heroin withdrawal was associated with a concomitant decrease in both slow-wave and REM sleep. Several studies have shown similar results in experimental animals although the time course of events was different [20, 22, 24]. The initial decrease in REM sleep on withdrawal days 1 - 3 has been reported to be followed by an increase in REM sleep on days 4 - 12 in rats [20, 22, 24]. The data in the present study showed a suppression of sleep on all recording days, with days 2 and 3 displaying the greatest sleep disturbances. The REM rebound effect was also not observed in this study even at 5 - 7 days into withdrawal. Thus, the REM rebound supposedly correlated with heroin and/or morphine withdrawal in humans must occur at a later time. It is interesting to note that the REM sleep rebound associated with methadone withdrawal occurred around the 10th to 13th week [8, 9]. Amphetamine withdrawal has also been associated with a REM sleep rebound of up to 2 months [41]. Lewis *et al.* [7] also reported long-term changes in REM sleep for up to six months following short-term heroin administration and withdrawal.

The decrease in slow-wave sleep reported in this study during the acute withdrawal phase was most significant for stage II, although stages III and IV were also reduced. A similar decrease in slow-wave sleep has been reported during morphine withdrawal in animals [22, 27]. By comparison, the acute phase of alcohol withdrawal has also been associated with a marked decrease in slow-wave sleep, particularly stages III and IV [42 - 44]. In addition, it was noted that during alcohol withdrawal, the patients seemed unable to maintain the sleeping condition and showed fragmentation of sleep evidenced by frequent awakenings. The data in this study also showed a similar pattern to the alcohol withdrawal syndrome. However, alcohol withdrawal did not show marked changes in REM sleep [43, 44]. Thus, even though both alcohol and morphine withdrawal show decreases in slow-wave sleep, the marked changes in REM sleep during heroin withdrawal suggest further differential actions of these drugs.

Some of the sleep disturbances observed in this study may be part of a more general disturbance of the central and/or autonomic nervous system functions associated with removal of a chronically depressant drug. Investigations of other physiological parameters during heroin withdrawal are needed to understand further the acute withdrawal syndrome and its effect upon these physiological systems.

Acknowledgements

This research was supported by National Institute of Drug Abuse grant DA01613 and U.S. Army Medical Research and Development Command Contract DAMD-17-75-C-5030.

References

1 J. H. Jaffe, Drug addiction and drug abuse. In L. S. Goodman and A. Gilman (eds.), *The Pharmacological Basis of Therapeutics*, 5th edn., Macmillan, New York, 1975, pp. 284 - 324.
2 W. R. Martin, Drug dependence. In J. R. DiPalma (ed.), *Drill's Pharmacology in Medicine*, 4th edn., McGraw-Hill, New York, 1971, pp. 362 - 378.
3 W. R. Martin and D. R. Jasinski, Physiological parameters of morphine dependence in man: Tolerance, early abstinence, protracted abstinence. *J. Psychiatr. Res.*, *7* (1969) 9 - 17.
4 H. L. Andrews, Brain potentials and morphine addiction. *Psychosom. Med.*, *3* (1941) 399 - 409.
5 D. C. Kay, Human sleep during chronic morphine intoxication. *Psychopharmacologia*, *44* (1975) 117 - 124.
6 C. K. Himmelsbach, Clinical studies of drug addiction: Physical dependence, withdrawal and recovery. *Arch. Intern. Med.*, *69* (1942) 766 - 777.
7 S. A. Lewis, I. Oswald, J. I. Evans, M. D. Akindele and S. L. Tompsett, Heroin and human sleep. *Electroenceph. Clin. Neurophysiol.*, *28* (1970) 374 - 381.
8 D. C. Kay, Human sleep and EEG through a cycle of methadone dependence. *Electroenceph. Clin. Neurophysiol.*, *38* (1975) 35 - 43.
9 W. R. Martin, D. R. Jasinski, C. A. Haertzen, D. C. Kay, B. E. Jones, P. A. Mansky and R. W. Carpenter, Methadone — A reevaluation. *Arch. Gen. Psychiatry*, *28* (1973) 286 - 295.
10 M. G. Robinson, R. C. Howe, N. W. Ream, H. W. Siegel and F. W. Hegge, Acute heroin withdrawal in Viet Nam. An immunochemical evaluation of excretion. *Clin. Pharmacol. Ther.*, *16* (1974) 303 - 309.
11 M. G. Robinson, R. C. Howe, J. G. Varni, N. W. Ream and F. W. Hegge, Assessment of pupil size during acute heroin withdrawal in Viet Nam. *Neurology*, *24* (1974) 729 - 732.
12 M. G. Robinson, H. W. Siegel, R. C. Howe, N. W. Ream and F. W. Hegge, Biochemical and clinical findings during acute heroin withdrawal in Viet Nam: A preliminary report. In J. M. Singh and H. Lal (eds.), *Drug Addiction*, Vol. 4, Futura Publishing Company, Mount Kisco, New York, 1974, pp. 79 - 95.
13 S. L. Baker, U. S. Army heroin abuse identification program in Viet Nam: Implications for a methadone program. *Am. J. Public Health*, *62* (1972) 857 - 860.
14 L. N. Robins, A follow-up of Viet Nam drug users. *Special Action Office for Drug Abuse Prevention Monograph*, Series A, Number 1, Executive Office of the President, Washington, D.C., 1973.
15 B. J. Rosenbaum, Heroin: Influence of method of use. *N. Engl. J. Med.*, *285* (1971) 299 - 300.
16 M. J. Sarg, Heroin use in the Navy. *N. Engl. J. Med.*, *286* (1972) 111 - 112.
17 D. C. Kay, R. B. Eisenstein and D. R. Jasinski, Morphine effects on human REM state, waking state, and NREM sleep. *Psychopharmacologia*, *14* (1969) 404 - 416.
18 D. C. Kay, Sleep and some psychoactive drugs. *Psychosomatics*, *14* (1973) 108 - 118.
19 B. K. Colasanti, Involvement of brain biogenic amines in the electroencephalographic and behavioural effects of morphine in post-addict rats. *Neuropharmacology*, *16* (1977) 235 - 240.
20 B. Colasanti, A. Kirchman and N. Khazan, Changes in the electroencephalogram and REM sleep time during morphine abstinence in pellet-implanted rats. *Res. Commun. Chem. Pathol. Pharmacol.*, *12* (1975) 163 - 172.
21 S. D. Echols and R. E. Jewett, Effects of morphine on sleep in the cat. *Psychopharmacologia*, *24* (1972) 435 - 448.
22 N. Khazan, The implication and significance of EEG and sleep–awake activity in the study of experimental drug dependence on morphine. In S. Ehrenpreis and A. Neidle (eds.), *Methods in Narcotics Research*, Marcel Dekker, New York, 1975, pp. 173 - 215.

23 N. Khazan and B. Colasanti, EEG correlates of morphine challenge in post-addict rats. *Psychopharmacologia, 22* (1971) 56 - 63.
24 N. Khazan and B. Colasanti, Protracted rebound in rapid eye movement sleep time and electroencephalogram voltage output in morphine-dependent rats upon withdrawal. *J. Pharmacol. Exp. Ther., 183* (1972) 23 - 30.
25 N. Khazan and C. H. Sawyer, Mechanisms of paradoxical sleep as revealed by neurophysiologic and pharmacologic approaches. *Psychopharmacologia, 5* (1964) 457 - 466.
26 P. Nash, B. Colasanti and N. Khazan, Long-term effects of morphine on the electroencephalogram and behavior of the rat. *Psychopharmacologia, 29* (1973) 271 - 276.
27 R. M. Post, Clinical aspects of cocaine: Assessment of acute and chronic effects in animals and man. In S. J. Mule (ed.), *Cocaine: Chemical, Biological, Clinical, Social, and Treatment Aspects*, CRC Press, Cleveland, 1976, pp. 203 - 215.
28 G. A. Young, J. E. Moreton, L. Meltzer and N. Khazan, REM sleep distributions in post-addict rats relapsing to morphine self-administration: Effects of Naloxone subcutaneous pellets. *Res. Commun. Chem. Pathol. Pharmacol., 11* (1975) 355 - 363.
29 G. A. Young, J. E. Moreton, L. T. Meltzer and N. Khazan, L-Alpha-acetylmethadol (LAAM), methadone and morphine abstinence in dependent rats: EEG and behavioral correlates. *Drug Alcohol Depend., 2* (1977) 141 - 148.
30 R. C. Howe and F. W. Hegge, Changes in sleep patterns associated with acute withdrawal from pure heroin. *Proceedings Sixth Annual Meeting of Society for Neuroscience*, Toronto, Canada, 1976, p. 894.
31 R. C. Howe, F. W. Hegge and J. L. Phillips, Effect of heroin withdrawal upon rapid eye movement (REM) sleep in humans. *Proceedings Eighth Annual Meeting of Society for Neuroscience*, St. Louis, Missouri, 1978, p. 540.
32 J. H. Jaffe and W. R. Martin, Narcotic analgesics and antagonists. In L. S. Goodman and A. Gilman (eds.), *The Pharmacological Basis of Therapeutics*, 5th edn., Macmillan, New York, 1975, pp. 245 - 283.
33 W. H. Oldendorf, S. Hyman, L. Braun and S. Z. Oldendorf, Blood–brain barrier penetration of morphine, codeine, heroin, and methadone after carotid injection. *Science, 178* (1972) 984 - 986.
34 A. Rectschaffen and A. Kales (eds.), *A Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects*, NIH Publication No. 204, U.S. Government Printing Office, Washington, D.C., 1968.
35 R. L. Ohler, Heroin use by veterans. *N. Engl. J. Med., 285* (1971) 692.
36 C. P. O'Brien, T. J. O'Brien, J. Mintz and J. P. Brady, Conditioning of narcotic abstinence symptoms in human subjects. *Drug Alcohol Depend., 1* (1975) 115 - 123.
37 G. Gianutos and H. Lal, Narcotic analgesics and aggression. *Mod. Probl. Pharmacopsychiatry, 13* (1978) 114 - 138.
38 J. A. Thornhill, M. Hirst and C. W. Gowdey, Changes in diurnal temperature and feeding patterns of rats during repeated injections of heroin and withdrawal. *Arch. Intern. Pharmacodyn., 223* (1976) 120 - 131.
39 M. Babbini, M. Gaiardi and M. Bartoletti, Changes in fixed-interval behavior during chronic morphine treatment and morphine abstinence in rats. *Psychopharmacologia, 45* (1976) 255 - 259.
40 N. Khazan, J. R. Weeks and L. A. Schroeder, Electroencephalographic, electromyographic and behavioral correlates during a cycle of self-maintained morphine addiction in the rat. *J. Pharmacol. Exp. Ther., 155* (1967) 521 - 531.
41 I. Oswald and V. R. Thacore, Amphetamine and phenmetrazine addiction. *Br. Med. J., ii* (1963) 427 - 431.
42 R. P. Allen, A. Wagman, L. A. Faillace and M. McIntosh, Electroencephalographic (EEG) sleep recovery following prolonged alcohol intoxication in alcoholics. *J. Nerv. Ment. Dis., 153* (1971) 424 - 433.
43 L. C. Johnson, J. A. Burdick and J. Smith, Sleep during alcohol intake and withdrawal in the chronic alcoholic. *Arch. Gen. Psychiatry, 22* (1970) 406 - 418.
44 J. W. Smith, L. C. Johnson and J. A. Burdick, Sleep, psychological and clinical changes during alcohol withdrawal in NAD-treated alcoholics. *Q. J. Stud. Alcohol, 32* (1971) 982 - 994.